REMARKS

Claims 8-23 and 25-35 have been withdrawn by the Examiner. Claims 1-7 and 24 have been rejected. Applicant cancels claims 2-4, 6-8, 10, 15-20, 26-27, and 30-33 without prejudice. Claims 1, 9, 11, 12, 13, 21, 24, 25, 28, 34, and 25 have been amended. Claims 36-51 are new. Support for amendments to claims 1, 9, and 21 can be found, for example, in the original claims. Support for the amendments adding the phrase "catalyzes a reaction in a metabolic pathway that produces an isoprenoid" to claim 1, 9 and 25 can be found, for example, in the descriptions at page 9, line 29 to page 10, line 9 and page 5, line 17. Support for the amendment to claim 24 adding the term "restriction polylinker" can be found, e.g., at page 3, line 21-24. Amendments to claims 11-13, 28, 34 and 35 merely change the respective claims from which these claims depend.

Applicant has added new claims 36-51. Support for new claims 36-40, 44-45, and 49 can be found, e.g., at page 14, line 12 to page 15, line 13. Support for new claims 41-43 can be found, e.g., at page 15, line 7. Support for new claims 46-48 can be found, e.g., at page 4, lines 28-31. Support for new claim 50 can be found, e.g., at page 2, line 31 and page 1, line 24 to page 2, line 1. Support for new claim 51 can be found, e.g., at page 7, line 15.

Reconsideration of the claims, as amended, is requested.

Traverse of the Withdrawal of Claims 8-21 and 25-35

The Examiner has withdrawn claims 8-21 and 25-35 because these claims are not drawn to the elected species of phosphoenopyruvate synthase (pps). Applicant respectfully traverses, and requests the Examiner's reconsideration. In responding to the Office Communication dated July 12, 2002, Applicant provisionally elected pps as a "heterologous polypeptide" for initial examination. The Examiner argues that pps is not a "required enzyme for the biosynthesis of any metabolite." Although the original claims contemplate pps as such an enzyme (see, for example, original claims 9 and 14), the Examiner interprets the term "required," not to mean required for a particular result, but to mean required in all circumstances. Because the Examiner's reading is inconsistent with the original claims, Applicant has amended the claims to

more clearly point out the claimed invention. As amended, claims 9, 11-14, 21, 25, 28, 29, 34, and 35 do encompass the elected species.

Written Description Rejection

The Examiner has rejected claims 1-7 and 24 for lack of written description. Although claims 1 and 24 have been amended to expedite prosecution, Applicant does not accede to the Examiner's written description rejection and reserves the right to argue the rejection in subsequent or other applications.

Applicant has amended claim 1 to require an *E. coli* host cell which is modified by mutation or deletion in *glnL* and includes a nucleic acid comprising a promoter bound by ntrC. One identifying characteristic of the host cell of claim 1 is that the promoter is bound by ntrC. Sevenich (IDS Item BR) and references cited therein describe methods for evaluating binding by ntrC and include exemplary sequences bound by ntrC. Since this information was well known to those skilled in the art prior to the filing of this application, a skilled artisan would recognize a promoter bound by ntrC without any difficulty. Another identifying characteristic of the host cell of claim 1 is a deletion or mutation of *glnL*. At the time of filing, *glnL* was a well characterized gene that a skilled artisan would recognize. See, e.g., Feng (IDS Item AL).

Applicant notes that what is conventional or well known to one of ordinary skill in the art need not be disclosed in detail ("Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112 ¶1, 'Written Description' Requirement," Federal Register, Vol. 66, No. 4, 1099, 1106 (2001). Moreover, Applicant is not limited to the five representative strains mentioned by the Examiner since the invention is described in such full, clear, concise, terms that a skilled artisan would recognize that Applicant was in possession of the invention when he filed this application. In addition to the identifying characteristics described above, Applicant notes that the fields of *E. coli* genetics[1] and DNA binding proteins[2] were among the most mature and highly skilled in biotechnology at the time of filing.

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[1] See, for example, *Escherichia coli and Salmonella: Cellular and molecular biology, Second edition,* Ed. F. C. Neidhardt, *et al.* ASM Press, Washington, DC, two volumes (1996).

[2] See, for example, *Transcriptional Regulation* (Cold Spring Harbor Monograph Series 22), Eds. Steven L. McKnight & Keith R. Yamamoto, Cold Spring Harbor Laboratory Press (1992).

Applicant has also amended claim 24 to require a *glnAp2* promoter and an *E. coli* host cell that is genetically modified by a deletion or mutation of a *glnL* histidine protein kinase gene. This claim is described in the specification, for example, at page 3, lines 24-26 in full, clear, concise, and exact terms. An example of the *glnAp2* promoter is described at page 2, lines 25-26.

Enablement Rejection

The Examiner has rejected claims 1-7 and 24 for lack of enablement. Although claims 1 and 24 have been amended to expedite prosecution, Applicant does not accede to the Examiner's enablement rejection and reserves the right to argue the rejection in subsequent or other applications. Since claims 1 and 24 have been amended as discussed above, Examiner's concerns about enablement should be obviated. Moreover, the Examiner's attention is again drawn to the high level of skill in the art and the teachings of the specification.

§ 102(a) Rejection based on Farmer

The Examiner has rejected claims 1-7 under 35 U.S.C. 102(a) in view of Farmer (2000). Applicant submits a Rule 132 Declaration which evidences that the disclosure in Farmer is derived from the applicant's own invention and respectfully requests that the rejection based on Farmer be withdrawn.

§ 102(b) Rejections based on Haldiman

The Examiner has rejected claim 1 under 35 U.S.C. 102(b) in view of Haldiman's teaching of *E. coli* bacterial strain BW24386. As amended, the host cell of claim 1 includes a nucleic acid encoding a heterologous polypeptide that catalyzes a reaction in a metabolic pathway which produces an isoprenoid. Since Haldiman does not disclose or suggest such a heterologous polypeptide, Haldiman cannot anticipate or make obvious claim 1.

§ 103 Rejections based on WO96/08567

The Examiner has rejected claims 1-7 and 24 as obvious over WO96/08567 ("Liao") in view of Bock, McCleary (AK), McCleary (AP), Haldiman, and Feng. The Examiner alleges, in part, as follows:

> [I]t would have been obvious . . . to link the production of pps to the presence of a metabolite in the cell which signals that significant amounts of carbon are being diverted away from the aromatic biosynthetic pathway. Liao [WO96/08567] teach that acetate production occurs under these conditions. Therefore, it would have been obvious . . . to replace the tac promoters [of WO96/08567] with a promoter which is induced by high acetate levels.

However, there is no motivation to combine these references, since, prior to this invention, acetate was generally considered detrimental to growth of bacterial cells and production of recombinant proteins. For example, Aristidou (IDS Item BL) states at column 1, page 475:

> Acetate is a lipophilic agent that is harmful to cell growth. Moreover, experimental results in our laboratory agree well with common observation that recombinant gene expression is greatly reduced for acetate accumulation above 15-25 mM.

Bauer (IDS Item BM) is to similar effect. See, for example, column 1, page 1296:

> Organic acids accumulate in the culture medium during aerobic growth of *Escherichia coli* on glucose. The most abundant organic acid is often acetic, and its concentrations can build up to levels that are inhibitory to growth. In a previous study, we showed that intracellular accumulation of interleukin-2 (IL-2) . . . was inversely correlated with cell density and acetate accumulation in fermentor cultures. These observations provided circumstantial evidence that acetate was at least partially responsible for the cessation of product accumulation during expression of heterologous genes in *E. coli* . . . .

Given these detrimental effects of acetate on recombinant protein production, one would not have been motivated to use a promoter that is regulated by acetyl phosphate to produce a heterologous polypeptide that catalyzes a reaction in a metabolic pathway which produces an isoprenoid. Applicant is unaware of any teaching in WO96/08567, Bock, McCleary (AK), McCleary (AP), Haldiman, and Feng to the contrary.

In WO96/08567, pps was induced prior to accumulation of acetate using promoters that were independent of acetate levels. Prior to the Applicant's invention, high acetate levels might

have been expected to impair production of a heterologous protein, such as pps, to the extent that sufficient pps would not be produced to counteract the accumulation of acetate. Thus, one would not have been motivated to combine WO96/08567 and Bock with McCleary (AK), McCleary (AP), Haldiman, and Feng. Only with the hindsight provided by this application can one conclude that a waste or starvation signal such as acetate should be used to induce expression of a heterologous polypeptide that catalyzes a reaction in a metabolic pathway which produces an isoprenoid.

For at least these reasons, applicant respectfully submits that the rejection of claims 1 and 24 based on WO96/08567 in view of Bock McCleary (AK), McCleary (AP), Haldiman, and Feng should be withdrawn.

Applicant submits that all pending claims are in condition for allowance.